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Environmental contaminants of emerging concern in seafood – European database on contaminant levels

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ABSTRACT

Marine pollution gives rise to concern not only about the environment itself but also about the impact on food safety and consequently on public health. European authorities and consumers have therefore become increasingly worried about the transfer of contaminants from the marine environment to seafood.

So-called “contaminants of emerging concern” are chemical substances for which no maximum levels have been laid down in EU legislation, or substances for which maximum levels have been provided but which require revision. Adequate information on their presence in seafood is often lacking and thus potential risks cannot be excluded. Assessment of food safety issues related to these contaminants has thus become urgent and imperative. A database (www.ecsafeseafooddbase.eu), containing available information on the levels of contaminants of emerging concern in seafood and providing the most recent data to scientists and regulatory authorities, was developed.

The present paper reviews a selection of contaminants of emerging concern in seafood including toxic elements, endocrine disruptors, brominated flame retardants, pharmaceuticals and personal care products, polycyclic aromatic hydrocarbons and derivatives, microplastics and marine toxins. Current status on the knowledge of human exposure, toxicity and legislation are briefly presented and the outcome from scientific publications reporting on the levels of these compounds in seafood is presented and discussed.

1. Introduction

Awareness is growing that oceans and seas can be a potential source of energy, raw materials and biomaterials for feed and food production among others. But before these potentialities can be exploited, we must have in-depth knowledge of the functioning of these marine systems and how to protect them against harm due to anthropogenic activities. One of the issues of highest priority is the pollution caused by chemical substances. Marine ecosystems can receive various chemical pollutants through rivers, direct discharges, or atmospheric deposition. These ecosystems are therefore the ultimate destination for a large group of chemicals with potential accompanying ecological hazards – and by extension also public health hazards. Hence, pollutants can be present in marine food items through accumulation in marine biota and the marine food web, with subsequent potential consequences for seafood safety. These hazards are nationally and internationally recognized by the scientific community and governmental food

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authorities. Therefore, several international monitoring programs have been developed, *e.g.* within the OSPAR Convention (The Convention for the Protection of the Marine Environment of the North-East Atlantic) (OSPAR, 1998) and the European Marine Strategy Framework directives (ED, 2008a). Besides that, European Food Safety Authority (EFSA) carries out risk assessments and writes scientific opinions on a wide range of chemicals present in food. These chemicals can originate from different sources such as food production and packaging, man-made activities or natural occurrence in the environment.

Seafood is one of the most important food commodities consumed worldwide. It is recognized as a high-quality and healthy food item. However, seafood, like other types of foodstuff, can also be a source of harmful environmental contaminants like polychlorinated biphenyls (PCBs), dioxins, residues of pesticides, toxic elements, new emerging contaminant, *etc*. (Domingo, 2007). The presence of contaminants in seafood for human consumption at levels above the regulatory level may have a negative impact on the health of consumers. Specific for seafood, maximum levels for a range of contaminants are laid down in the legislation and monitoring programs guarantee that seafood is regularly examined for the presence of a selection of environmental contaminants. So far, the focus has mainly been on well-known chemical pollutants such as polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), certain marine toxins and certain toxic elements. Nevertheless, there is an increasing demand for knowledge about the presence and potential effects of the so-called “contaminants of emerging concern” in seafood (Lopez de Alda et al., 2003; Wille et al., 2012).

Contaminants of emerging concern in seafood are substances that are gaining increasing interest by the scientific community and regulatory authorities. They are new substances for which no maximum levels have been laid down in EU legislation and for which a potential risk cannot be excluded. The list of emerging contaminants may also include previously identified compounds for which maximum levels have been laid down but which need revision due to new hazard information. The group of emerging pollutants includes pharmaceuticals, personal care products, hormone disrupting substances, brominated flame retardants, toxic elemental species, *etc*. Because of the persistence, bioactivity and bioaccumulation potential of several of these substances, concern is increasing about the possible harmful effects on ecosystems and human health. These contaminants are candidates for future regulation, depending on their toxicity, potential health effects, public perception and monitoring data regarding their occurrence.

The information currently available on the levels of several emerging environmental contaminants in seafood is rather fragmented and is not harmonized which may hinder the elaboration of seafood risk assessment. Therefore, a unique European database (www.ecsafeseafooddbase.eu), based on information collected from scientific literature, reports and monitoring programs concerning emerging contaminants levels in seafood, was developed within the ECsafeSEAFOOD project (www.ecsafeseafood.eu). The ECsafeSEAFOOD database platform has been developed in Wordpress, a free and open source content management system based on PHP and MySQL. Almost 400 papers about contaminants of emerging concern are available in the online database platform. This database is an innovative and useful monitoring tool for seafood risk assessment that enables the contaminants to be prioritized for monitoring in seafood.

This review was prepared using the information available in the database. It comprises a selection and discussion of contaminants of emerging concern in seafood, including toxic elements, endocrine disruptors, brominated flame retardants, pharmaceuticals and personal care products, PAH derivatives, microplastics and marine toxins. The following sections contain an overview of the current knowledge on human exposure, toxicity and legislation of each group of contaminants. Some sections include a table that summarizes a selection of relevant published studies regarding seafood contamination with these contaminants. The referred concentrations are min–max and/or mean values depending on the reported concentration in the publication.

2. Toxic elements and elemental species

Contamination with toxic elements is a worldwide recognized public health hazard because these pollutants are widespread in the environment from either natural (*e.g.* mineral weathering, volcanic activies) or anthropogenic sources (*e.g.* agricultural practices, industrial release) (Olmedo et al., 2013). Elements may change their chemical form in the environment, but they cannot be degraded over time. This means that they are environmentally persistent and may bioaccumulate in plants and animals (Nadal et al., 2008; Martorell et al., 2011).

Some elements have nutritional functions essential to life (*e.g.* selenium, iodine and zinc) and for maintenance of a good health status in humans and animals. In contrast, other elements, *e.g.* lead, cadmium and mercury, have no nutritional properties and intake of these elements can lead to severe adverse health effects. In 2010 the World Health Organization (WHO) listed four elements (arsenic, lead, mercury and cadmium) on their prioritized list of the top ten chemicals of major public health concern (WHO, 2010). These elements, and other elements with toxic properties, are often named “heavy metals” a well-known term in the general population. However, due to contradictory definitions in the literature and lack of coherent scientific basis, the term is not accepted in the scientific community (Duffus, 2002). An alternative term is “toxic elements”. Although this term neither has general scientific consensus nor an exact definition, it seems to be more broadly accepted and is therefore used here (Hajeb et al., 2014).

Toxic elements can occur in food, either because of their natural presence in the environment or from contamination during food production, processing and storage. Fish and shellfish have been identified as the food items typically showing the highest concentrations of a number of toxic elements (Llobet et al., 2003; Bocio et al., 2005). The maximum levels of certain elements (lead, cadmium and total mercury) in certain types of seafood are regulated by the European Commission regulation 1881/2006 (ECR,2006a amended by ECR (2008,2011a,2014)). For other toxic elements, no maximum levels have been laid down in the European legislation, partly due to a lack of information about their presence in seafood.

Chronic exposure to toxic elements may cause several adverse effects to human health, even at relatively low quantities (Sharma and Agrawal, 2005) as summarized by Goyer and Clarkson (1996). From a toxicological point of view, the chemical form (*i.e.* the elemental speciation) in which the element is ingested may play a significant role. For example, methylmercury is considered to be much more toxic than inorganic mercury compounds, while inorganic arsenic is considered to be more toxic than the organic species of arsenic (EFSA, 2009a, 2012a; Francesconi, 2007). Knowledge about the chemical form(s) of certain elements present in seafood is therefore required in order to improve assessment of seafood safety beyond simply knowing the total elemental amount. In addition, in some cases toxic elements are only regulated for certain edible tissues in seafood (*e.g.* cadmium in crustaceans' white meat). However, other tissues are being increasingly consumed as delicatesses; some of these may accumulate heavy metals but they are not regulated due to insufficient information (*e.g.* cadmium in crustaceans' brown meat). Several dietary exposure assessments have been conducted in recent years

Table 1
Toxicological guideline values established by EFSA and JECFA.

Element/species	Body	Year	Type	Value
Metals				
Mercury, inorganic	JECFA	2011a	PTWI	4 μg/kg bw/week
	EFSA	2012a	TWI	4 μg/kg bw/week
Methylmercury	JECFA	2003	PTWI	1.6 μg/kg bw/week
	EFSA	2012a	TWI	1.3 μg/kg bw/week
Lead	JECFA	2011b	PTWI	Withdrawn, no no-effect level identified
	EFSA	2010c	PTWI	Withdrawn, no no-effect level identified
			BMDL$_{01}$	0.50 μg/kg bw/day (developmental neurotoxicity)
Cadmium	JECFA	2011b	PTMI	25 μg/kg bw/month
	EFSA	2009c	TWI	2.5 μg/kg bw/week
Arsenic, inorganic	JECFA	2011a	BMDL$_{0.5}$	3 μg/kg bw/day (2–7 μg/kg bw/day)
	EFSA	2009a	BMDL$_{01}$	0.3–8 μg/kg bw/day (lifetime risk)
Pharmaceuticals and personal care products				
Benzylpenicillin	JECFA	1990	ADI	< 30 μg/kg bw
Oxytetracycline	JECFA	2002	ADI	0–30 μg/kg bw
Emamectin	JECFA	2013	ADI	0–0.5 μg/kg bw
Derquantel	JECFA	2012	ADI	0–0.3 μg/kg bw
Flumequine	JECFA	2006a, 2006b	ADI	0–30 μg/kg bw
Carazolol	JECFA	1995	ADI	0–0.1 μg/kg bw
Dexamethasone	JECFA	2009	ADI	0–2 μg/kg bw
Tilmicosin	JECFA	1998	ADI	0–40 μg/kg bw
Triclabendazole	JECFA	1993	ADI	0–3 μg/kg bw
Tylosin	JECFA	2009	ADI	0–30 μg/kg bw
Avilamycin	JECFA	2009	ADI	0–2 μg/kg bw
Endocrine disruptors				
Bisphenol A	EFSA	2015	TDI	4 μg/kg bw
Estradiol-17β	JECFA	2000	ADI	0–0.05 μg/kg bw
Testosterone	JECFA	2000	ADI	0–2 μg/kg bw
Progesterone	JECFA	2000	ADI	0–30 μg/kg bw
Melengestrol acetate	JECFA	2001	ADI	0–0.03 μg/kg bw
PFOS	EFSA	2008a	TDI	150 ng/kg bw/day
PFOA	EFSA	2008a	TDI	1500 ng/kg/bw/day
Polycyclic aromatic hydrocarbons				
Benzo[a]pyrene	JECFA	2005	BMDL$_{10}$	0.10–0.23 mg/kg bw/day
Benzo[a]pyrene	EFSA	2008c	BMDL$_{10}$	0.07–0.20 mg/kg bw/day
Benzo[a]pyrene and chrysene (PAH2)	EFSA	2008c	BMDL$_{10}$	0.17–0.45 mg/kg bw/day
Benz[a]anthracene, benzo[a]pyrene, benzo[b]fluoranthene and chrysene (PAH4)	EFSA	2008c	BMDL$_{10}$	0.34–0.93 mg/kg bw/day
benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[ghi]perylene, benzo[a]pyrene, chrysene, dibenz[a,h]anthracene, and indeno[1,2,3-cd]pyrene (PAH8)	EFSA	2008c	BMDL$_{10}$	0.49–1.35 mg/kg bw/day
Brominated flame retardants				
Pentabromodiphenyl ether	EFSA	2011a	LD$_{50}$	2640–6200 mg/kg bw
Polybrominated biphenyls	EFSA	2010d	LD$_{50}$	> 1000 mg/kg bw (single exposure) 64–150 mg/kg bw (after repeated exposure)
Hexabromocyclododecane	EFSA	2012b	NOEL	10 mg/kg bw (cited Ema et al. (2008))
Tetrabromobisphenol A	EFSA	2011b	BMDL$_{10}$	16 mg/kg bw
1,2-Bis(2,4,6-tribromophenoxy)ethane	EFSA	2012c	LD$_{50}$	> 10 g/kg for rats and dogs

ADI: acceptable daily intake; BMDL: benchmark dose lower limit of the 90% confidence interval; LD: lethal dose; NOEL: no-observed-effect level; PTMI: provisional tolerable monthly intake; PTWI: provisional tolerable weekly intake; TDI: tolerable daily intake; TWI: tolerable weekly intake.

and toxicological guideline values have been established for some of the toxic elements, including arsenic (inorganic), cadmium, lead and mercury (inorganic and methylmercury) by EFSA and JECFA (Table 1). For all elements certain consumer groups, which had exposure levels close to or even exceeding the guideline values, were identified. Hence, there is a need for continued monitoring and compilation of data on toxic elements in food groups, in order to continuously improve risk assessment and to identify food groups, which contribute mostly to the dietary intake.

Data on levels of seafood-relevant toxic elements (and their elemental species of highest toxicological concern) in fish and other types of seafood are summarized in Supplementary Table S1.

The concentrations of total arsenic (As) in marine species vary widely depending on factors such as species type, sampling location and feeding regime. The highest values for total As are typically observed in species of shellfish reaching values up to 50 mg/kg wet weight (ww) (De Gieter et al., 2002; Sirot et al., 2008; Anacleto et al., 2009), whereas in fish typically lower levels are reported. The hepatopancreas and gonad tissues are reported to contain the highest values in crustaceans (Barrento et al., 2008; Marques et al., 2010). In order to evaluate seafood safety, data for inorganic As, the most toxic form of As, must be considered. In fish the concentration of inorganic As is in most cases in the low ppb range, whereas higher levels are typically reported for shellfish where even concentrations of several mg/kg have been reported in extreme cases (Sloth and Julshamn, 2008). The data emphasizes the need for selective data on inorganic As levels for improved risk assessment of seafood safety in relation to As.

For cadmium (Cd) the concentration range is very wide, depending on the species and tissues studied as well as the sampling location. Since Cd target organs are the viscera, the highest values are typically observed in the liver of some fish (Costa et al., 2009; Raimundo et al., 2013) and the hepatopancreas of crustaceans, reaching values of up to 30.0 mg/kg (Barrento et al., 2009a). For muscle tissue, in most species the maximum level of EU legislation (1.0 mg/kg) is not exceeded (ECR, 2014). However, in some contaminated estuarine areas, some bivalve molluscs may exceed this maximum level (Lourenço et al., 2006). Hence, population groups with a high consumption of bivalves from such areas are at risk of exceeding the toxicological guideline value for Cd.

Generally, lead (Pb) values are below the legal maximum levels for most types of seafood species (fish, crustaceans and molluscs). The values found for muscle tissues are between “not detected” and 0.55 mg/kg ww (Falcó et al., 2006; Perelló et al., 2008; Nadal et al., 2008; Martorell et al., 2011; Olmedo et al., 2013). The fact that the recent reported values are lower than in years 1950–80 indicates that the contamination sources have declined over recent decades, largely due to the ban of the use of Pb additives in gasoline. In general, seafood is not a major contributor to lead dietary intake.

Mercury (Hg) is one of the most analyzed contaminants worldwide. Given the potential of Hg to bioaccumulate and biomagnify in marine food webs, its concentration varies greatly from species to species and also depends on the contamination of the catching area. Thus, Hg levels in fish can range from “not detected” to values of 20 mg/kg ww (Andersen and Depledge, 1997; Miklavčič et al., 2011; Spada et al., 2012; Zmozinski et al., 2014). The highest values are typically found in carnivorous and predatory species (Andersen and Depledge, 1997; Storelli et al., 2003; Brambilla et al., 2013; Koenig et al., 2013). Several studies indicate that the predominant form of Hg in fish is the most toxic form, methylmercury (Cardoso et al., 2010; Afonso et al., 2013; Miniero et al., 2013; Olmedo et al., 2013). However, European legislation does not yet include limits for this mercury species. Seafood is the major dietary source of mercury exposure and some studies state that special attention to methylmercury exposure must be emphasized because some consumer groups may have a higher estimated intake of methylmercury than the recently established Tolerable Weekly Intake value of 1.3 μg/kg bw/week (EFSA, 2012a; Miniero et al., 2013; Ruiz-de-Cenzano et al., 2014; Dellatte et al., 2014).

3. Endocrine disruptors

Organic pollutants exhibiting endocrine disrupting activity (Endocrine Disrupting Compounds – EDCs), as bisphenols, alkylphenols, estrogens and perfluorinated compounds, are prevalent over a wide range in the aquatic ecosystem. In recent years, there is a growing interest in these compounds due to their ability to interfere with the endocrine system of different organisms, causing important alterations in development. For example, estrogenic chemicals can bind or activate the estrogen receptor and are consequently responsible for feminization of males (Routledge and Sumpter, 1996;Desbrow et al., 1998).

As information on the occurrence of endocrine disruptors in marine biota is limited some freshwater studies are included in this review. Supplementary Table S2 summarizes the levels of endocrine disruptors in marine biota and seafood and Supplementary Table S3 summarizes levels in freshwater biota.

3.1. Bisphenols

Bisphenols are a group of chemical compounds with two hydroxyphenyl functionalities. Bisphenol A (BPA), the most common representative of this group, is used in epoxy resins and polycarbonate plastics that are employed in surface coatings for food cans and in food contact materials.

It is well known that BPA has an estrogenic activity. It is believed that BPA could be associated with reproductive cancers (testicular, prostate, breast, uterine, ovarian, and so forth), fertility problems (low sperm count, decreased sperm quality) and other endocrine related consequences (Vandenberg et al., 2007).

Regardless of the ubiquitous presence of BPA in the environment, the primary source of human exposure to the compound is through the diet, as a result of the migration of the BPA monomer from the packaging. Related to this, BPA is permitted for use in food contact materials in the European Union under Regulation 10/2011/EU (ECR,2011b). Dietary exposure assessment has been recently evaluated by the EFSA and a scientific opinion on the risk to public health related to the presence of BPA in foodstuff has been released (EFSA, 2015). In this report a temporal TDI of 4 μg/kg bw per day was established (Table 1). It was concluded that the dietary exposure to BPA for the highest exposed groups, which include infants children and adolescents, is below the temporal TDI indicating that there is not health concern for BPA at the estimated levels of intake. Air, dust, and water exposition are other possible sources of exposure. A limited number of studies (Supplementary Tables S2 and S3) exist on the occurrence of BPA in biota and seafood (Cunha et al., 2011; Vandenberg et al., 2007). The levels of BPA found in marine and freshwater biota range from below the LOD to 213.1 ± 20.2 ng/g ww for seafood (Basheer et al., 2004) and 224 ng/g dw for freshwater fish (Jakimska et al., 2013).

3.2. Alkylphenols and their ethoxylates

Alkylphenol polyethoxylates (APEs) consist of a branched-chain alkylphenol that has reacted with ethylene oxide to produce an ethoxylated chain. They have excellent surface active properties and are used in large quantities as surfactants for industrial, agricultural, and domestic applications like household cleaning detergents, personal care products, pharmaceuticals, pesticide formulations, textiles, paints, pulp and paper industries, oil recovery and mining (Céspedes et al., 2008; Ferrara et al., 2008).

APEs reach the environment mainly through industrial and urban wastewater and are transformed by microorganisms to alkylphenols (especially nonylphenols and octylphenols). Alkylphenols (APs) are important intermediates in the production and degradation of polyethoxylates. In aquatic environments and particularly in the sea, their high persistence results in bioaccumulation which leads to the transfer to higher levels in the food chain (Vazquez-duhalt et al., 2005; Ferrara et al., 2008).

Human uptake of APs and nonylphenol (NP) in particular can result from different routes, *e.g.* inhalation, ingestion of contaminated food and dermal absorption. The oral intake *via* seafood, water supply and food contaminated *via* leaching from packaging may be significant (Inoue et al., 2001; Ferrara et al., 2005, 2008).

Mueller and Kim (1978) demonstrated that APs are able to displace estradiol from the estrogen receptor. The estrogenic properties of NP and octylphenol (OP) have been demonstrated in *in vitro* and *in vivo* studies (Ferrara et al., 2005).

Because of these endocrine disrupting effects and their ubiquitous occurrence, NP and OP have been included as priority pollutants in the European Water Framework Directive (ED, 2000, 2008b) and a drastic policy of emission reduction has been implemented. Since 2005, the marketing and use of products and product formulations that contain more than 0.1% of nonylphenol ethoxylate (NPE) or NP is restricted in the EU (ED, 2003). Despite worldwide actions to restrict their use, they are still found in water and sediments in high amounts. The presence of alkylphenols including NPs and OPs has been reported in freshwater and marine molluscs, fish and even in crustaceans ranging from non-detected levels up to 1431 ng/g ww (Ferrara et al., 2005) in marine biota and up to 1119 ng/g dw in freshwater biota (Verslycke et al., 2005).

3.3. *Perfluoroalkyl substances*

Perfluoroalkyl substances (PFASs) are characterized by a fluorinated hydrophobic carbon chain attached to one of the more hydrophilic end groups. They are surfactants with an exceptional stability and capacity for lowering surface tension. These useful properties have encouraged their use in many industrial and consumer applications including stain- and water-resistant coatings for fabrics and carpets, oil-resistant coatings for paper products approved for food contact, fire-fighting foams, mining and oil well surfactants, floor polishes, and insecticide formulations (EFSA, 2008a; Hrádková et al., 2010; Kantiani et al., 2010). This has led to the widespread distribution of these chemicals in the environment and a subsequent opportunity for widespread human exposure.

Elevated concentrations of perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), two of the most common produced PFASs in human blood have been linked to a number of potential health effects, including immunotoxicity, neurotoxicity, reproduction and developmental toxicity, endocrine disruption and carcinogenesis (Stahl et al., 2011). The half-life of PFOS and PFOA in humans is estimated at 5.4 years and 3.8 years respectively (Olsen et al., 2007).

Due to their persistence, bioaccumulation and toxicity (PBT) features and global distribution the EU banned most uses of perfluorooctane sulfonate (PFOS) and related compounds in 2008 (ED, 2006). The Scientific Panel on Contaminants in the Food Chain (CONTAM) established a Tolerable Daily Intake (TDI) for PFOS of 150 ng/kg body weight per day and 1500 ng/kg body weight for PFOA (perfluorooctanoic acid) (Table 1; EFSA, 2008a). In May 2009 PFOS was included in Annex B of the Stockholm Convention on persistent organic pollutants (SCPOP, 2009; Hrádková et al., 2010). Furthermore, PFOS has been included as priority pollutant in the European Water Framework Directive (ED, 2000, 2008b) and an environmental quality standard (EQS) has been set at 9.1 ng/g wet weight for PFOS in biota. Despite these restrictions, related chemicals which potentially may degrade to PFOS or other PFASs are not yet regulated (Jogsten et al., 2009).

Dietary intake is one possible route of human exposure to PFOS or other PFASs. Bioaccumulation in fish and shellfish has been shown to be the main source of PFASs in the diet (Noorlander et al., 2011). In biota, the amphiphilic PFASs tend to bind to serum proteins and accumulate in blood and protein rich tissues of exposed organisms. This is especially true for the longer perfluorinated chainlength compounds ($CF2 > 7$) since bioaccumulation factors increase with perfluor chainlength (Kwadijk et al., 2010). In this way, these compounds are biomagnified in the food chain. Food preparation is another source of dietary contamination (Berger et al., 2009; Kantiani et al., 2010; Tittlemier et al., 2007).

Data on levels of PFASs in marine and freshwater biota are summarized in Supplementary Tables S2 and S3, respectively. Studies show that PFOS is usually the predominant PFAS with concentrations ranging from < 0.02 to 877 μg/kg wet weight in heavily polluted areas (van de Vijver et al., 2003; Miège et al., 2012; Kwadijk et al., 2010; Campo et al., 2015; Tittlemier et al., 2007; Berger et al., 2009). Therefore, levels frequently exceed the EQS for PFOS. This is especially true for freshwater systems. Levels detected in eel from 21 aquatic systems in the Netherlands indicate that the EQS was exceeded at nearly all sampling locations (Kwadijk et al., 2010). The high levels of PFOS detected can be attributed to industrial activities, although the pollution does not extend further downstream (Campo et al., 2015). Studies on marine fish also typically find PFOS as predominantly PFAS usually with levels in the lower ng/g (Jogsten et al., 2009; de Voogt et al., 2008; Hrádková et al., 2010; Munschy et al., 2013; Eriksson et al., 2013; Domingo et al., 2012; Wille et al., 2011; So et al., 2005) although higher levels (tens of ng/g) are also registered (Llorca et al., 2009; Gulkowska et al., 2006; Nania et al., 2009). Especially high levels have been reported for PFOS in marine molluscs (up to 1225 ng/g dw) and crustaceans (up to 877 ng/g ww) (Kannan et al., 2002; van de Vijver et al., 2003). During the period 2006–2012 EFSA performed an occurrence study in 13 European countries. The most frequently quantified PFAS was PFOS with levels of 0.04–211 μg/kg in fish meat, 0.09–65 μg/kg in crustaceans and 0.02–2.9 μg/kg in molluscs. PFASs lower bound mean concentrations in fish were compared in relation to their aquatic environment. Results showed constantly higher mean concentrations in freshwater fish compared to diadromous or marine fish while diadromous fish had mean concentrations slightly higher or similar to marine fish (EFSA, 2012d).

3.4. *Estrogens*

Natural estrogens (*e.g.* estrone, 17β-estradiol and estriol) are important for the function of the female sex organs. Synthetic compounds are used in medicine, as contraceptives and in some hormonal therapies (*e.g.* 17α-ethinylestradiol), or in veterinary medicine, as growth promoters of farmed animals (*e.g.* diethylstilbestrol). Their (human and animal) excretion together with their incomplete removal in sewage treatment plants, have caused the presence of several estrogens and related compounds in the aquatic environment (Young et al., 2004; Noppe et al., 2007). Several studies also report the bioaccumulation of estrogens in fish (Al-Ansari et al., 2010; B. Huang et al., 2013). Adverse effects such as vitellogenesis, feminization and hermaphrodism in fish but also breast, prostate and testicular cancer in humans have been widely reported (J. Liu et al., 2011).

In 2012, the European Commission proposed the inclusion of 15 additional priority substances in the European Water Framework Directive (ED, 2000, 2008b); amongst them are 17β-estradiol and 17α-ethinylestradiol. Regarding to food safety the European Union established Directive 96/22/EC (EC, 1996) amended by Directive 2008/97/EC (EC, 2008a) concerning the prohibition on the use in stockfarming of certain substances having a hormonal or thyrostatic action and of beta-agonists. The scope of the Directive is open to all food-producing animals with substances having oestrogenic, androgenis or gestagenic action being prohibited such as oestradiol 17β and its ester-like derivates. The EFSA opinion of 2007 (EFSA, 2007) reported ADI levels for some hormones (Table 1) but the report is foscused on bovine meat and meat products with seafood remaining in oblivion.

Estrone, estriol, 17α-ethinylestradiol, and 17β-estradiol are the estrogens reported thus far in marine and freshwater fish and molluscs, both in wild and farmed organisms, reaching a maximum concentration of 38 ng/g dw in marine bivalves (Pojana et al., 2007).

4. Brominated flame retardants (BFRs)

Flame retardants (FRs) comprise a large number of chemical substances that are widely used at relatively high concentrations in many industrial and household products, as well as during manufacture of electrical/electronic equipment, textiles and plastic polymers, primarily to improve their fire resistance (Merlani, 2010). FRs are incorporated as either additives (interleaved within the material to be flame retarded) or reactive ingredients (combined into the oligomers or polymers being manufactured) (Bergman et al., 2012). Additive FRs are believed to be more easily released into the environment than the reactive ones (Segev et al., 2009).

Two main categories of FRs can be identified: inorganic products often based on metallic hydroxides; and organic compounds based on bromine, chlorine, phosphorus, nitrogen and boron. The brominated, chlorinated, and phosphorus-containing flame retardants cover the major proportion of organic FRs, although some products contain neither halogen nor phosphorus atoms (*e.g.* melamine, 1,3,5-triazine-2,4,6-triamine) (Bergman et al., 2012).

Currently, because of their high performance efficiency and low cost, the largest market group of FRs is the brominated flame retardants (BFRs) group (Segev et al., 2009). BFRs consist of chemicals with a variety of physicochemical properties and uses (EFSA, 2012c). Bergman et al. (2012) identified and reported 55 established, emerging, novel and/or potential BFRs, though this list does not include either congeners or enantiomers of a given FR. For instance, PBDEs include 209 congeners. In general, BFRs are characterized by moderate to very high octanol–water partition coefficient (log Kow), with few exceptions, once more corroborating their lipid-solubility and consequent easy bioaccumulation.

This chemical family has been progressively getting more special attention, mainly after the discovery of their occurrence in the environment, including feed and food, and in human biota. Unfortunately, few data exist on the presence of BFRs in humans and its toxic effects. Nevertheless, for some classes, as polybrominated diphenyl ethers (PBDEs), effects on the neurological and thyroid hormone systems, sexual hormones and reproduction have been shown in rodents (L. Chen et al., 2012; Lee et al., 2012; Williams et al., 2013). There are also indications that exposure to hexabromocyclododecanes (HBCDDs) can affect the liver hormone system and might cause neurobehavioral alterations (Deng et al., 2009; Feng et al., 2013), while tetrabromobisphenol A (TBBPA) has also been shown to have effects on thyroid hormones, neurological function, and reproduction (Chan and Chan, 2012; G.Y. Huang et al., 2013).

Since 2002, the European Directive 2002/96/EC on waste electrical and electronic equipment (WEEE) requires that plastic containing BFRs have to be removed from any separately collected WEEE and treated separately (ED, 2002a). In addition, in 2010 various amendments of the original European Union Regulation No. 850/2004 (ECR, ,2004a) came into force and new chemicals were added to the list of prioritary persistent organic pollutants, including some BFRs, namely four PBDEs (Tetra-, Penta-, Hexa- and Hepta-PBDEs) and hexabromobiphenyl (ECR, ,2010b, 2010c). Afterwards, the 8th Persistent Organic Pollutants Review Committee (POPRC) also proposed the inclusion of total HBCDDs in Annex A of the Convention (SCPOP, 2012).

The following classes of BFR were defined by EFSA (EFSA, 2011a) as the most relevant in terms of toxicological effects and prevalence, thus being the main focus of the present section: (1) PBDEs; (2) polybrominated biphenyls (PBBs); (3) hexabromocyclododecanes (HBCD); (4) hexabromobenzene (HBB); (5) TBBPA and other phenols, as tribromophenol (TBP); (6) decabromodiphenyl ethane (DBDPE); and (7) 1,2-Bis(2,4,6-tribromophenoxy)ethane (BTBPE).

In general, for all emerging and novel BFRs there is a lack of basic information on their occurrence in food as well as a lack of information on toxicokinetics and toxicodynamics (EFSA, 2012c). However, for some BFRs a toxicological guidance value is established (Table 1).

BFR-treated products, whether in use or in waste, can release BFRs into the environment and consequently contaminate the air, soil and water. Unfortunately, these contaminants may then find their way into the food chain. They occur mainly in food of animal origin (predominantly fish and derived products) and can cause toxic effects to human health. Seafood contamination is examined below by providing detailed information about each class of BFRs of concern. Detailed reviews related to physicochemical characterization, major sources, environmental fate and toxicity can be found in the papers of Oost et al. (2003), Daley et al. (2014), and Cruz et al. (2015).

4.1. Polybrominated diphenyl ethers (PBDEs)

PBDEs are highly lipophilic substances, though slightly lower than the most halogenated PBBs (Braekevelt et al., 2003). Their molecular weights range from 249 (BDE-1, BDE-2, and BDE-3) to 959 (BDE-209). PBDEs are non-ionisable compounds and present low volatility (EFSA, 2011a).

Many PBDEs are strictly regulated for commercialized mixtures and articles, but there is no legislation concerning their presence in seafood products. As defined in the European Commission Decision 2005/717/EC (ECD, 2005), Deca-BDE can no longer be used in electronics and electrical applications in Europa since July 2008, and a maximum level of 0.1% of total PBDEs by mass in homogeneous materials shall be tolerated (ECD, 2009). In 2009, the Commission Regulation No. 552/2009 updated the restriction conditions for Penta-BDE and Octa-BDE, set in ANNEX XVII of this Regulation (ECR, ,2009a). As a consequence, these cannot be placed on the market or used as substances, in mixtures or in articles, at concentrations higher than 0.1% by mass. Since 2010, all PBDEs from tetra- to hepta-BDEs are regulated by the global Stockholm Convention and are scheduled for elimination (SCPOP, 2006).

Several papers have been published in recent years regarding seafood contamination with PBDEs (Cruz et al., 2015). PBDE congeners that are more frequently analysed and found to be present in greater amounts in seafood, regardless of the selected analytical methodology, are #47, 99, 100, 153, 154, 183 and 209, all included in the list of those already under regulation (ECR, ,2009a; ECD, 2009). In particular, BDE-47 is commonly the most concentrated pollutant in seafood, reaching up to 81800 ng/g lipid weight (lw) in mud carp as reported by Wu et al. (2009). A possible reason for this could be the higher environmental up-take efficacy for BDE-47. Debromination into lower congeners and other metabolites can occur during metabolism or in the environment as a result of either microbial activity or photodegradation.

In general, highest levels of total PBDEs are detected in benthic or benthopelagic species as common carp, with up to 108,000 ng/g (Echols et al., 2013), followed by burbot with 45,144 ng/g (Mariussen et al., 2008), 32,900 ng/g (Berg et al., 2013), and Chinese loach with 16,963 ng/g (Qin et al., 2009), all expressed on a lipid weight (lw) basis. The differences observed in PBDE profiles can be related with metabolic differences, age of fish and lipid content, and other physiological differences among fish species.

4.2. Polybrominated biphenyls (PBBs)

The 209 possible PBB congeners have molecular weights similar to those of PBDEs, ranging from 233 to 943, depending on the number of bromine substitutions. With the increasing degree of bromination, PBBs become more lipophilic compounds, thus achieving lower vapour pressures and lower water solubility.

PBBs are established FR additives that were produced until the mid-1980s, except Deca-BB which was produced until 2000. According to the Directive 2002/95/EC of the European Parliament and of the Council of 27 January 2003, new electrical and electronic equipment put on the market after 1 July 2006 should not contain PBBs (ED, 2002b). In effect as of 9 October 2012, the consolidated version of Regulation No. 1907/2006 amendments defines the conditions of PBB restrictions, in fact only regarding Hexa-BB congeners, set in ANNEX XVII to this Regulation (ECR, ,2006b). In 2010, during the Conference of the Parties of the Stockholm Convention, hexabromobiphenyl as well as all PBDEs were classified as a POP of strict elimination (SCPOP, 2012).

Despite not being currently manufactured, PBBs are still present in both biotic and abiotic samples, due to their environmental persistence. Only few studies in the past decade focused their assessment in seafood (*e.g.*Cruz et al., 2015). A study from the UK revealed the presence of PBB in a large number of fish, shellfish and crustacean samples obtained in the UK in 2006 (FSA, 2006). The authors reported data on three non-ortho congeners (#77, 126, and 169) and seven orthocongeners (#15, 49, 52, 80, 101, 153 and 209). Gierón et al. (2010) documented that the concentrations of PBBs in North Sea fish such as salmon, carp, gilthead seabream and grey gurnard were higher than in fish from the Baltic Sea. The highest total PBB concentration was measured in carp muscle tissue (635 ± 107 pg/g ww) and the lowest was in carp muscle samples (0.567 ± 0.245 pg/g). In contrast, Malavia et al. (2011) found no PBBs in similar samples of fish collected in the Spanish market. As reported by Cruz et al. (2015) PBB 153 is the congener most often analyzed due to its high persistence in the environment, being also the one that reaches higher levels.

4.3. Hexabromocyclododecane (HBCD)

HBCDs are established BFRs formed *via* addition of bromine to 1,5,9-cyclododecatriene, consisting mainly of three stereoisomers (α-, β- and γ-HBCD) substituted with six bromine atoms in the cyclododecane molecule (EFSA, 2011a).

HBCDs are additive BFRs that have been used for many years; they can be effective alternatives for PBDEs in some applications. Despite not being legislated for seafood, HBCDs application is receiving more attention from regulatory authorities. Currently all three main isomers are included in Annex XIV of the amended Regulation No. 1907/2006, which lists substances subject to authorization (ECR, 2006b).

Several papers have reported the levels of total HBCD or their individual congeners in seafood (Cruz et al., 2015). In marine fish, HBCD range from the lower ng/g level (Morris et al., 2004; Janák et al., 2005; Ueno et al., 2006; Kakimoto et al., 2008) up to 688.79 ng/g (Y. Zhang et al., 2013). Significant differences of the HBCD content in biota even from adjacent sampling areas were observed (Morris et al., 2004; Remberger et al., 2004; Janák et al., 2005). As reported in several studies, α-HBCDD is the predominant stereoisomer (Covaci et al., 2006; Köppen et al., 2010; Y. Zhang et al., 2013; Malarvannan et al., 2014) indicating its higher bioaccumulative potential (EFSA, 2011b).

The Panel on Contaminants in the Food Chain (CONTAM Panel) concluded that current dietary exposure to HBCDs in the European Union does not raise a health concern (EFSA, 2012b).

4.4. Tetrabromobisphenol A (TBBPA) and other brominated phenols

TBBPA has a high lipid solubility and a low volatility. Similar to TBBPA, other brominated phenols are technically produced by bromination of phenol to contain 2, 3 or 5 bromine substituents (EFSA, 2012c) such as 2,4-DBP and 2,4,6-TBP. In comparison to other BFRs, 2,4-DBP and 2,4,6-TBP are less lipophilic and more volatile.

TBBPA is known to be the highest-volume BFR in the world, representing about 60% of the total BFR market (EFSA, 2011b). However, to date none of the previously mentioned brominated phenols (TBBPA, 2,4-DBP and 2,4,6-TBP) are regulated under any specific regulation for their use or production, without even any maximum tolerance levels in foodstuffs.

Occurrence data on TBBPA and its derivatives in seafood is scarce; only about 12 scientific papers have been published in the last 10 years (Cruz et al., 2015). TBBPA was measured in fish from the North Sea by Morris et al. (2004) from 1998 to 2001 with levels ranging from 5.0 (common whelk, whole) to 245 ng/g lw (whiting, muscle). Lower levels in fish were, however, reported by Harrad et al. (2009), Shi et al. (2009), He et al. (2013) and Hloušková et al. (2013) with concentrations ranging from 0.32 to 1.7 ng/g lw, 0.541 to 2.044 ng/g lw, 6.5 to 66 ng/g lw and 0.14 to 4.43 ng/g ww, respectively. In general, the LOQ was reported to be <1 ng/g ww (EFSA, 2011b).

Despite being detected in many environmental samples, the Panel on Contaminants in the Food Chain (CONTAM Panel) concluded that current dietary exposure to TBBPA in the European Union does not raise a health concern (EFSA, 2011b).

4.5. Hexabromobenzene (HBB)

HBB is an emerging BFR and an aromatic perbrominated compound that may undergo nucleophilic aromatic substitution with strong nucleophiles and reductive debromination under environmental conditions (EFSA, 2011b).

Until now, HBB is not regulated in EU under any specific regulation for their use or production (ECR, ,2006b; ESIS, 2014), nor even regarding maximum tolerance levels in foodstuffs. The limited number of scientific papers on this pollutant in seafood is therefore understandable, with about 6 publications between 2004 and 2014, most from Asiatic countries, as reported by Cruz et al. (2015). Nevertheless, in Europe, Munschy et al. (2011) determined amounts of HBB in muscle tissue and liver of common sole (*Solea solea*) from 2007 to 2009 that ranged from 0.0003 to 0.1994 ng/g ww. These levels were far below those reported in freshwater fish from China, *i.e.* 197–2451 ng/g lw despite those fish having been collected from a pond on an electronic waste recycling site (Wu et al., 2010). Arp et al. (2011) analysed fish liver, crab and blue mussel samples from three places in Norway, but HBB could not be found above the method LOQ (0.1 ng/g ww).

4.6. Decabromodiphenyl ethane (DBDPE)

DBDPE has a polybrominated character with lipid soluble features and a low volatility (EFSA, 2012c).

It was introduced in the mid-1980s, becoming commercially significant as an alternative to BDE-209. Nevertheless, its presence in seafood literature is scarce. Hitherto, DPDBE is not regulated under any specific regulation for their use or production, nor even regarding maximum tolerance levels in foodstuffs.

DBDPE was detected in fish (mud carp, nile tilapia, plecostomus) at concentrations ranging from 27 to 230 ng/g lw (He et al., 2012), which were comparable to the levels reported in other fish and crustaceans (crucian carp, prawn, common carp) collected from a pond in an electronics company waste site in South China (338 ng/g lw) (Wu et al., 2010). These levels are 2 orders of magnitude higher than levels found in fish from Lake Winnipeg, Canada (3.30 ng/g lw) (Law et al., 2006). Zhou et al. (2010) did not find DBDPE above the LOQ (0.020 ng/g) in any of the 22 samples collected in the five Great Lakes and two lakes in Canada.

4.7. 1,2-Bis(2,4,6-tribromophenoxy)ethane (BTBPE)

Common to the remaining BFRs, BTBPE is a lipid-soluble contaminant of low volatility. BTBPE is an additive FR that has been produced since the mid-1970s. Similar to DBDPE, only few research articles are available concerning BTBPE in seafood. Such as other BFRs, BTBPE is also not regulated under any specific regulation for their use or production, without any maximum tolerance levels in foodstuffs.

BTBPE was measured in common sole muscle and liver from an estuary of the River Seine with levels ranging from 0.00004 to 0.0724 ng/g ww (Munschy et al., 2011). These concentrations were three orders of magnitude lower than the mean concentrations in the muscle of various fish species from Lake Winnipeg, Canada, which were between 0.026 and 3.72 ng/g lw (Law et al., 2006). In trout from Lake Ontario, Canada, BTBPE concentrations increased between 1979 and 1993, then decreased to around 1.6 ng/g ww until 2004 (Ismail et al., 2009). In southern China, BTBPE was found at levels between <0.012 ng/g lw and 0.105 ng/g lw in the muscle of freshwater fish collected near to an electronic waste processing area (Shi et al., 2009), whereas Wu et al. (2010) reported much higher values (*i.e.* 1.71–518 ng/g lw). Zhou et al. (2010) did not find BTBPE above the LOQ (0.011 ng/g w.w.) in any of the 22 fish samples collected in the five Great Lakes and from two lakes in Canada.

Tables summarizing published papers and levels of brominated flame retardants in seafood were presented in Cruz et al. (2015).

5. Pharmaceuticals and personal care products

Pharmaceuticals and personal care products (PPCPs) are a diverse group of chemicals used in veterinary medicine, agricultural practice, human health and cosmetic care. Pharmaceuticals include pharmaceutically active compounds from different therapeutic groups like antibiotics, psychiatric drugs, analgesics/anti-inflammatory drugs, tranquilizers, calcium channel blockers, diuretics, *etc*. Personal care products (PCPs) can be grouped into the following main classes: disinfectants, fragrances, insect repellents, preservatives and UV filters (Brausch and Rand, 2011; Hao et al., 2007).

The PPCPs can enter aquatic ecosystems from municipal wastewater treatment plant discharges, run off from agricultural areas that utilize veterinary therapeutics, and releases from aquaculture sites (Brooks et al., 2005; Cabello, 2006). An incessant load of these chemicals thus enters the aquatic system. As a result they have been increasingly detected in the environment during the recent years (Hao et al., 2007; Kolpin et al., 2002; Nikolao et al., 2007; Gros et al., 2013; Collado et al., 2014).

Pharmaceuticals are designed to target specific metabolic and molecular pathways in humans and animals. They can act at very low concentrations, which raises concern about their potential to cause adverse effects on wildlife and on consumers through the ingestion of contaminated seafood.

Several studies have demonstrated that environmental exposure to PPCPs may result in the accumulation of parent compounds, their metabolites or both in tissues of aquatic organisms (Ramirez et al., 2007; Huerta et al., 2012a). The relevance of metabolites and transformation products when studying bioaccumulation of pharmaceuticals in organisms has been previously pointed out, as they can show equal or higher bioaccumulation capabilities (Boxall et al., 2004; Huerta et al., 2012b). The polar nature of most pharmaceuticals make them directly bioavailable to filter-feeding organisms such as bivalves (McEneff et al., 2014; Bueno et al., 2013; Klosterhaus et al., 2013; Li et al., 2012). They filter large quantities of surface water for feeding and breathing and consequently are more susceptible to these chemicals. Shellfish are food commodities consumed worldwide, and in some cases even eaten raw (*i.e.* oyster). Their widespread consumption therefore calls for exhaustive quality control.

Another source of accumulation of PPCPs in seafood is the prophylactic or therapeutic use of pharmaceuticals in aquaculture (marine or freshwater systems) to prevent or treat parasitic and microbial diseases. Residues of these drugs can remain in tissues, creating the potential for exposures of consumers (Cabello, 2006).

The presence of pharmaceuticals in seafood may potentially act as a risk to consumers either through direct effect of allergy and toxicity, or indirectly through potential microbial resistance (Cabello, 2006). Therefore the European Commission has set maximum residue limits (MRLs) for a variety of pharmaceuticals in foodstuffs of animal origin (ECR, 2010a). The authorized substances included in this regulation regarding seafood cover anti-infectious and anti-parasitic agents commonly used in aquaculture. There is also a list of prohibited substances including some antibiotics like chloramphenicol, ronidaloze, metronidazole, *etc*. (ECR, 2010a). However, there is a wide set of other pharmaceuticals (of different therapeutic families) released to the environment, that have been detected in fish and mollusk and might also need regulation (Supplementary Table S3).

The joint FAE/WHO Expert Committee on Food additives (JECFA) has regular meetings dedicated to the evaluation of veterinary drug residues in food. Since 1968 nineteen meetings have been held for establishing acceptable daily intakes (ADIs) and for recommending MRLs. A wide set of compounds has already been under consideration and some others are currently being considered. A selection of some examples is given in Table 1.

Studies on pharmaceuticals and personal care products in seafood are scarce. For this reason studies on freshwater biota are also integrated in this paper. The levels of PPCPs in marine and in freshwater biota reported in literature are summarized in Supplementary Tables S4 and S5, respectively.

Analgesics and anti-inflammatory drugs have been found in marine and freshwater fish and molluscs. The most commonly detected compounds are acetaminophen/paracetamol, diclofenac and salicylic acid, with concentrations ranging between 4.1 and 490 ng/g dw (Wille et al., 2011; Huerta et al., 2012a; Klosterhaus et al., 2013). Gemfibrozil, a lipid regulator, was detected in liver of freshwater fish at levels of 90 ng/g (Ramirez et al., 2009).

The psychiatric drugs are the most studied group of pharmaceuticals. Liver is the main target organ for freshwater fish, showing concentration levels up to 10-fold higher than in muscle fillets. Carbamazepine was found in marine molluscs and freshwater fish fillets at concentrations ranging from 0.8 to 5.3 ng/g ww (Ramirez et al., 2007; Klosterhaus et al., 2013) and in fish liver up to 8 ng/g liver. Citalopram and desmethylcitalopram were found in freshwater molluscs and fish fillets at 97 ng/g ww (Du et al., 2014) and in fish livers at 600 ng/g ww. Diazepam and sertraline were also found in liver at 110 and 545 ng/g, respectively (Maruya et al., 2012; Ramirez et al., 2009). Fluoxetine and norfluoxetine were detected in several studies and were found in fish livers at concentrations of 86 and 130 ng/g ww, respectively (Du et al., 2012; Ramirez et al., 2009).

Levels of diphenhydramine, a histamine H1 and H2 receptor antagonist, were reported in several studies with maximum levels of 11.1 ng/g ww in liver and 1.32 ng/g in fillet (Ramirez et al., 2007, 2009). The β-blocking agents, carazolol and propranolol, were found in fish up to 3.8 and 4.2 ng/g dw, respectively and 63 ng/g dw in molluscs (Huerta et al., 2012a, 2012b; Wille et al., 2011). Diltiazem, a calcium channel blocker, was found in fish livers at 0.9 ng/g and caffeine, a stimulant drug, was only detected in one study at 4.5 ng/g ww (Ramirez et al., 2009; Wang and Gardinali, 2012).

Residues of antibacterial and antifungal compounds have been widely elucidated in molluscs, but were also reported in fish. Triclosan and methyltriclosan, triclocarban, sufamethoxazole, ofloxacin and erythromycin were the most relevant compounds found at concentrations up to 507 and 1010 ng/g lw, 157 ng/g lw, 20 ng/g dw, 242 ng/g dw and 18 ng/g dw, respectively (Ramaswamy et al., 2011; Li et al., 2012; Rüdel et al., 2013; McEneff et al., 2014).

The increasing use of musk fragrances in cosmetic industry entailed the entry of these compounds in the trophic chain. The European Union has prohibited the use of some musks (musk ambrette, musk moskene and musk tibetene) in cosmetic products.

Despite prohibition of these nitro musks, farmed fish contaminated with musk moskene and musk ambrette were detected, with levels of 1.93 and 14.6 ng/g ww, respectively (Duedahl-Olesen et al., 2005). Other musks (musk xylene, musk ketone and tonalide) have been restricted (ED, 1998, 2008c; ECR, ,2009b). Although regulated, musk ketone and musk xylene were found at maximum concentrations of 1800 ng/g lw and 1060 ng/g lw, respectively (Rimkus and Wolf, 1995; Gatermann et al., 2002). During the past decades, polycyclic musks have replaced the market for nitro musks. Hence, the concentrations of this group of fragrances are commonly higher than the nitro forms. Galaxolide (HHCB) and Tonalide (AHTN) are the most studied polycyclic musks, with concentrations reaching 160 and 45 μg/g lw, in molluscs and fish, respectively (Gatermann et al., 2002). European Commission carried out a human health risk evaluation of HHCB including the indirect exposure through the environment (including food and water) at the local scale as well as at the regional scale, concluding that there was no evidence of health concern (EC, 2008b). Similarly, the European Chemicals Agency (ECHA) assessed the indirect human health risk derived from the environment and concluded: “There is at present no need for further information and/or testing and no need for risk reduction measures beyond those, which are being applied already” (ECHA, 2005). To the best of our knowledge, neither governmental organizations nor scientific panels have proposed a tolerable daily intake value or oral reference dose for musk compounds to date.

Parabens are used as preservatives in the food, cosmetic, and pharmaceutical industries. Methylparaben, propylparaben, ethylparaben, butylparaben and benzylparaben have been found in seafood at maximum levels of 3600, 1100, 840, 70 and 2.5 ng/g, respectively (Ramaswamy et al., 2011; Liao et al., 2013).

Literature on the occurrence of UV filters in seafood is scarce, but indicates that seafood can be contaminated with UV stabilizers (Mottaleb et al., 2009; Kim et al., 2011; Bachelot et al., 2012).

6. Polycyclic aromatic hydrocarbons (PAHs) and derivatives

Although PAHs are routinely monitored compounds, great concern about their presence in food persists. On September 2012, a new law came into force that restricts the presence of PAHs in foodstuff. Where previously only benzo(a)pyrene was analyzed, now foodstuffs must be screened for benzo(a)pyrene, benzo(a) anthracene, benzo(a)fluorantheen and chrysene. In addition, the maximum residue levels allowed for PAHs in fish, crustaceans and molluscs were reduced (ECR, 2011c). Moreover, it has been recognized that the priority PAHs are not the only important polycyclic aromatic compounds; PAH derivatives may also contribute significantly to the load of toxic contaminants and may pose risks to human health (Lundstedt et al., 2007).

The toxic effects of PAHs have been the subject of many studies and they are known as toxic, mutagenic and carcinogenic compounds. The EFSA CONTAM Panel concluded that eight PAHs (benzo[a]pyrene, benz[a]anthracene, benzo[b]fluoranthene, benzo[k]fluoranthene, benzo[ghi]perylene, chrysene, dibenz[a,h]anthracene and indeno[1,2,3-cd]pyrene), either individually or in a combination, are currently the only possible indicators of the carcinogenic potency of PAHs in food. Based on these eight PAHs toxicological guidance values were determined (Table 1; EFSA, 2008c). Less is known about the toxicity of PAH derivatives like oxygenated PAHs and alkylated PAHs. Nevertheless, several studies have shown that a number of oxygenated PAHs (oxy-PAHs) (oxidation products of PAHs) are acutely toxic to a variety of organisms. Oxy-PAHs have also been shown to induce oxidative stress, endocrine system disruptions, cytotoxic effects and mutagenic effects. In many cases the oxy-PAHs are more toxic than their parent compounds (Lundstedt et al., 2007). Although oxy-PAHs are considered to be potentially more hazardous than their parent compounds, knowledge on their concentration levels in seafood is limited. The scarce data available suggest a high degree of contamination, however. Layshock et al. (2010), for instance, showed oxy-PAHs concentrations in mussel tissue being higher than PAH concentrations. While the total concentration of the 16 United States Environmental Protection Agency (US EPA) priority PAHs was *ca.* 190 ppb, a selection of 9 oxy-PAHs was measured at a total concentration of *ca.* 280 ppb. In addition, Bandowe et al. (2014) showed that concentrations of the $\sum$15 oxy-PAHs (28–1715 ng/g) in fish muscle were higher than the $\sum$16 US-EPA PAHs (71–481 ng/g).

Toxicity data for alkylated PAHs (alkyl-PAHs) is also limited but, Sun et al. (2014) has demonstrated that alkylated PAHs may have greater toxicity than their parent compounds. Accurate quantification of alkyl-PAHs is difficult because of the lack in the availability of commercial standards for many of the individual isomers (Yang et al., 2014). Alkylated PAHs have been found in fish and shellfish from sites contaminated by crude oil. In general, the mass of the alkyl-PAHs in the tissues was higher than the mass of the parent non-alkylated PAHs (Baird et al., 2007).

7. Microplastics

Microplastics (plastic particles smaller than 5 mm) are ubiquitous in various environmental compartments: the water column, sediment and biota. They enter the environment from both primary and secondary sources. Primary sources include particulates which are produced either for direct use, such as for industrial abrasives, exfoliants and cosmetics, or as precursors (resin pellets) for the production of consumer products. Secondary sources relate to the formation of microplastics in the environment due to the degradation of larger plastic material (Arthur et al., 2009; Browne et al., 2007, 2011; Piha Henna et al., 2011).

Ingestion, accumulation and translocation of microplastics were demonstrated for diverse filter feeders such as eastern oyster (*Crassostrea virginica*), blue mussel (*Mytillus edulis*) and zebra mussel (*Dreissena polymorpha*) (Browne et al., 2008; Farrell and Nelson, 2013; Lei et al., 1996; Von Moos et al., 2012; Ward and Kach, 2009; Wegner et al., 2012; De Witte et al., 2014). This suggests the potential ability of microplastics to accumulate in higher trophic levels, as observed for the littoral crab after feeding on exposed mussels (Farrell and Nelson, 2013). The increasing scientific evidence that various marine species ingest and accumulate microplastics is an indication that these particles are entering the marine food chain (Van Cauwenberghe and Janssen, 2014).

The lack of standard methods and units to quantify microplastics complicates comparison between studies and limits the available knowledge on seafood contamination. Supplementary Table S4 summarizes the available publications concerning the occurrence and quantification of microplastics in fish and seafood. Mathalon and Hill (2014) detected microplastics in wild and farmed mussels: on average 178 microfibres per farmed mussel compared to 126 microfibres per wild mussel. These plastic body burdens are a lot higher than the concentrations reported by De Witte et al. (2014), Van Cauwenberghe and Janssen (2014), and Van Cauwenberghe et al. (2015), 2.6–5.1 total fibres/10 g ww, 0.36 ± 0.07 particles/g ww and 0.2 ± 0.3 particles/g ww respectively. Studies performed on fish revealed plastics in 2.6–36.5% of the examined fish (Dantas et al., 2012; Foekema et al., 2013; Lusher et al., 2013; Rummel, 2014; Sanchez et al., 2014) while Murray and Cowie (2011) detected microplastics in the stomach of 83% of the examined crustaceans (Supplementary Table S6).

In the current literature there are no reports on human *in vivo* or *in vitro* toxicity studies. It can be predicted that ingested microplastics will interact with molecules in the gut (Powell et al., 2010). However, knowledge is still lacking about whether this may lead to adverse effects. Another potential risk arises from leachable additives and adhering persistent contaminants. Widely used additives added during manufacture of plastics, such as phtalates and bisphenol A, are known as endocrine disruptors (Teuten et al., 2009; Van Cauwenberghe and Janssen, 2014). Besides that, hydrophobic persistent organic pollutants adsorb onto microplastic surfaces from seawater because of the low polarity of the plastic surfaces. Toxicity data of these persistent organic contaminants are well established and have been translated into food regulations (*e.g.*ECR, ,2011c, 2011d), but the question remains unanswered whether plastic mediated transfer of Persistent Organic Pollutants to organisms is possible (Mato et al., 2001; Hollman et al., 2013).

8. Marine toxins

Marine toxins, originating from marine microalgae (phytoplankton or benthic microalgae), can accumulate in fish, shellfish and other marine organisms. These toxins can cause diseases in humans that range from gastrointestinal to cardiologic and to neurological problems by eating of fish and shellfish (Hallegraeff, 1995). The present incidence of human intoxications is very difficult to assess. The Food and Drug Administration (2012) recognizes the lack of good statistical data on the occurrence and severity of shellfish poisoning by marine toxins. Previous figures had reported an incidence of over 60,000 cases per year (Van Dolah, 2000). However these figures should be revised presently. For instance, statistics for ciguatera cases only have reported between 50,000 and 500,000 cases per year (Fleming et al., 2008; Glaziou and Legrand, 1994; Lehane and Lewis, 2000).

Marine toxins are produced by unicellular algae that, in response to favorable conditions in their environment, may proliferate to form dense concentrations of cells or “blooms”. Only about 2% of more than 5000 known phytoplankton species have the capacity to produce potent toxins. Among toxic microalgae, most species belong either to dinoflagellates or diatoms (Hallegraeff, 1995; Daranas et al., 2001; Van Dolah, 2000).

During the past decades, the occurrence of harmful algal blooms has increased, both in frequency and in geographic distribution, along with the number of toxic compounds found in the marine food chain (Hallegraeff, 1995; Van Dolah, 2000).

Phytoplankton is crucial food for filter-feeding shellfish, as well as for the larvae of commercially important crustaceans and herbivorous fish. These organisms at the lowest levels of the food webs may act as vectors of toxins to humans (*e.g.* shellfish) although transfer of the toxins to higher trophic levels occurs (Van Dolah, 2000; Daranas et al., 2001).

Currently in the EU, maximum permitted levels (MPL) have been set for six groups of marine toxins in shellfish: Domoic acid group (DA, MPL: 20 mg/kg) as Amnesic Shellfish Poisoning (ASP) toxins, Saxitoxin group (STX, MPL: 800 μg/kg) as Paralytic Shellfish Poisoning (PSP) toxins, Okadaic acid (OA, MPL: 160 μg/kg) group, Pectenotoxin (PTX, MPL: 160 μg/kg) group, Yessotoxin (YTX, MPL: 3750 μg/kg) group and Azaspiracid (AZA, MPL: 160 μg/kg) group, all belonging to the lipophilic toxin group (ECR, ,2004b). Although EFSA had considered possible revision of regulatory levels for these families of toxins, levels on YTXs were only recently changed to higher levels.

In addition to toxins for which regulatory levels have been determined, concern exists for emerging toxins for which regulation does not specify maximum permitted levels (*e.g.* ciguatoxins) or for which regulation does not exist (cyclic imines, palytoxins, brevetoxins and tetrodotoxins). Also, azaspiracids constitute a group of interesting toxins that need further studies. AZAs are regulated toxins for which additional toxicological information is necessary due to their relatively recent discovery.

Supplementary Table S7 summarizes a small selection of occurrence of the different marine toxins in fish and seafood.

8.1. *Cyclic imines*

Spirolides (SPXs), gymnodimines (GYMs), pinnatoxins (PnTXs), and pteriatoxins (PtTXs) are marine toxins, present in shellfish and produced by dinoflagellates, belonging to the group of cyclic imines (CIs) (EFSA, 2010a; Paredes et al., 2011). They are grouped together due to similarities in their chemical structure (imino group as their common pharmacophore) and toxicity in mice (Cembella and Krock, 2008; EFSA, 2010a). Although they trigger high intraperitoneal toxicity in rodents these substances have not been categorically linked to human intoxication and the amount of cyclic imines in shellfish is not regulated (EFSA, 2010a; Otero et al., 2011). Nevertheless, since their mechanism of action includes effect on nicotidinic acetylcholine receptors, and their presence in seafood seems to be quite widespread, CIs should be considered as emerging toxin in order to understand their potential long-term effect on public health (Stivala et al., 2015).

In Europe, SPXs have been detected in a number of countries, while GYMs have been reported in shellfish from Croatia (Aasen et al., 2005; Villar González et al., 2006; Pigozzi et al., 2008; Gladan et al., 2011). GYMs have a global distribution: they have been found in shellfish from Tunisia (Biré et al., 2002) and New Zealand (Munday, 2014). In 2010, PnTXs were identified for the first time in shellfish in Europe (Miles et al., 2010). Recent findings suggest that PtTXs are transformed from PnTXs in shellfish, but PtTXs have not been reported in shellfish in Europe (Paredes et al., 2011).

8.2. *Ciguatoxins*

Ciguatoxins, which accumulate mainly in tropical and subtropical fish, are lipid-soluble polyether compounds produced by dinoflagellates from the genus *Gambierdiscus* spp. (EFSA, 2010b). This family of toxins causes Ciguatera Fish Poisoning (CFP) which is linked to a wide variety of gastrointestinal, neurological or cardiovascular symptoms, depending on the particular variety of the toxin.

During the last 10 years, ciguatoxins have been identified for the first time in fish (*Seriola* spp.) caught in European waters of Macaronesia (Madeira and Canary Islands) (Pérez-Arellano et al., 2005; Gouveia et al., 2009) and the microalgae *Gambierdiscus* spp. have also been described in the Mediterranean sea (Aligizaki and Nikolaidis, 2008). In the context of the European Common Fisheries Policy this potential hazard raises concern (Caillaud et al., 2010). In the European Union, limits are not stated while in other parts of the world some countries have regulations or management guidelines for CTX-group toxins in fish. The United States Food and Drug Administration (US FDA) has for example proposed guidance levels of < 0.1 µg/kg C-CTX-1 equivalents and < 0.01 µg/kg P-CTX-1 equivalents (EFSA, 2010b).

8.3. Palytoxins

Palytoxin (PlTX)-group toxins are complex polyhydroxylated compounds with both lipophilic and hydrophilic areas in their chemical structure. They have mainly been detected in marine zoanthids (soft corals) of the genus *Palythoa* and dinoflagellates of the genus *Ostreopsis* (Paredes et al., 2011).

Blooms of *Ostreopsis spp*. have recently been reported in several European countries. This occurrence may result in contamination of shellfish species intended for human consumption (Aligizaki et al., 2008; Ciminiello et al., 2006; EFSA, 2009b; Aligizaki et al., 2011).

Symptoms of palytoxin poisoning are not well-defined, but include myalgia and weakness, possibly accompanied by fever, nausea and vomiting (Deeds and Schwartz, 2010). Fatal cases have been reported after consumption of crabs and sardines (Ramos and Vasconcelos, 2010). Currently there are no regulations on PlTX-group toxins in shellfish, either in the EU, or in other

regions of the world but EFSA has proposed a maximum permitted level of 250 µg/kg shellfish (EFSA, 2009b).

8.4. Azaspiracids (AZAs)

AZAs are nitrogen-containing polyether compounds which have a chemical structure consisting of a spiral ring that contains a heterocyclic amine and an aliphatic carboxylic acid moiety (EFSA, 2008b). Incidents of shellfish poisoning in humans have particularly occurred in northern Europe and several species of dinoflagellates of the genus *Azadinium* spp. (Krock et al., 2009a; Tillmann et al., 2009) and *Amphidoma languida* (Krock et al., 2012) have been reported as AZA producers.

AZA poisoning is characterized by symptoms such as nausea, vomiting, diarrhea and stomach cramps (EFSA, 2008b). Annex III to Regulation (EC) No. 853/2004 establishes that live bivalve molluscs placed on the market for human consumption must not exceed the limit of 160 µg of AZA equivalents per kilogram (ECR, ,2004b). Due to on-going identification of new AZAs, AZA metabolites, and conversion products during cooking, all with unknown toxicity and occurrence, they are included in the group of emerging marine toxins.

8.5. Tetrodotoxin (TTX)

TTX consists of a positively charged guanidine group and a pyrimidine ring with six hydroxyl groups (Lee and Ruben, 2008). This toxin has been isolated from several species of puffer fish (Tetraodontidae family) but studies have also revealed its wide distribution in both terrestrial and marine animals (Yasumoto et al., 2006; Paredes et al., 2011). The origin of TTX in puffer fish, has been ascribed to endo-symbiotic bacteria naturally inhabiting the fish gut. Several bacterial species including *Pseudomonas* and *Vibrio* have been shown to produce TTXs (Bane et al., 2014).

In 2007, a case of TTX poisoning in Malaga (Spain) was reported after consumption of the sea snails *Charonia lampas lampas* imported from Portugal (Rodriguez et al., 2008). The species *Lagocephalus sceleratus* has been shown to enter the Mediterranean through the Canal of Suez. They contain low levels of TTXs and have caused fatal poisoning in Israel (Bentur et al., 2008). Later, this species was detected in areas further west in Greece (Katikou et al., 2009), Tunisia (Ben Souissi et al., 2014) and Italy (Azzurro et al., 2014).

TTX is a neurotoxin, specifically blocking voltage-gated sodium channels of nerve fibers. Toxicity can lead to weakness or paralysis and even death (Cohen et al., 2009).

TTX or its analogues are not regulated in the European legislation. However, according to the current EU legislation, fish belonging to the poisonous family of fish Tetraodontidae or products derived from it are not allowed on the European markets (ECR ,2004b, 2004c).

9. Conclusions

A diet rich in seafood presents a variety of nutritional benefits, but it can also be a source of pernicious environmental contaminants. Ingesting contaminated seafood provides a pathway for human exposure to environmental contaminants with a potential risk for human health.

In order to assess food safety issues related to contaminants of emerging concern in seafood and evaluate their impact on public health, a variety of objectives must be fulfilled (Fig. 1). Among these objectives is gathering the available information required for risk assessment. The present review summarizes concentration levels of contaminants of emerging concern in seafood. Since the concentrations of several substances in seafood have not yet been properly determined (*e.g.* almost all studies of pharmaceuticals and personal care products have been done on freshwater fish only), monitoring programs of such contaminants in seafood should be prioritized in the future. In addition, detailed seafood consumption data is necessary to assess actual human health risks. Furthermore, the toxicological data of emerging contaminants is still scarce for several compounds and the toxicological impact of these contaminants needs further assessment. When all of this required information is available, improved risk assessments can be performed and mitigation strategies can then be implemented.

The ECsafeSEAFOOD project focus on the above mentioned issues. Ongoing studies in the framework of this project are collecting data on contamination, consumption and toxicity in order to evaluate the impact of these contaminants of emerging concern

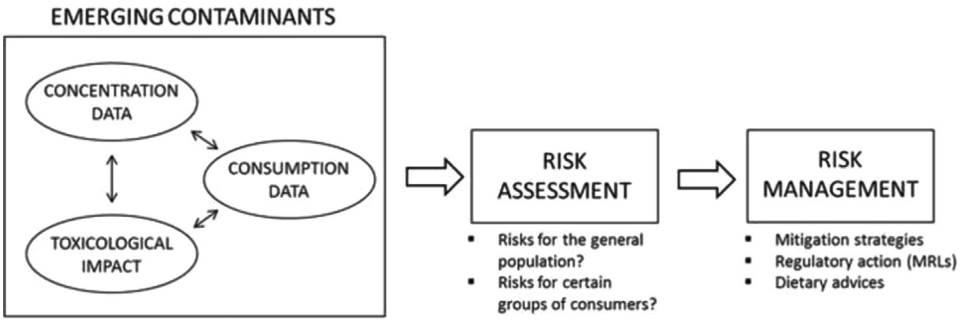

Fig. 1. Overview of relevant factors for the risk evaluation of contaminants of emerging concern.

on public health. This information is gathered in the online database platform (www.ecsafeseafooddbase.eu) in order to create an up-to-date information source. It is a useful tool for seafood risk assessment that can be consulted by the scientific community and regulatory authorities.

The outcome of ECsafeSEAFOOD will help to provide safe seafood and to reduce human health risks. This will enable European consumers and authorities to be more confident about the safety of their seafood.

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Appendix A. Supplementary material

Supplementary material associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2015.06.011.

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